REMARKS

The claims have been presented again because claim 15 in the August 5, 2003 Preliminary Amendment was incomplete. Accordingly, a new Listing of the Claims has been presented. Claims 1-14 were cancelled in the August 5, 2003 Preliminary Amendment, which is reflected in the above Listing of the Claims. Original claims 15-22 remain pending in the captioned application.

Obviousness Rejections

1. Claims 1 and 9 were rejected under 35 USC §103(a) as being unpatentable over U.S. Pat. No. 5,541,227 ("Loew") in view of PCT Appl. No. WO 91/16043 ("Mapelli") further in view of U.S. Pat. No. 5,780,046 ("Humber"). (December 8, 2004 Office Action ("Office Action") at 4.)

For the reasons set forth below the rejection, respectfully is traversed.

Claims 1 and 9 were cancelled in the August 5, 2003 Preliminary Amendment. Accordingly, it is believed that this rejection is moot. Therefore the rejection is improper and should be withdrawn.

2. Claims 1-22 were rejected under 35 USC § 103(a) as being unpatentable over Loew in view of Mapelli further in view of U.S. Pat. No. 4,835,187 ("Reuter") (Office Action at 5.)

Loew discloses

[57] **ABSTRACT**

An ibuprofen-containing medicament which contains ibuprofen only in the (S)-(+)-form is disclosed. (S)-(+)-ibuprofen is more than twice as active as the racemate which has until now been used in the treatment of rheumatism. This permits reduction of the quantity of active ingredient and the size of the tablets or dragees.

Ibuprofen, i.e. 2-(4-isobutylphenyl)-propionic acid is a tried and tested NSAR from the group of phenyl propionic acid derivatives that has shown itself to be effective in inhibiting prostaglandin synthesis in experiments with animals with inflammation. In therapy of humans, ibuprofen reduces pain, swelling and fever caused by inflammation. It shows the usual unwanted side effects of NSAR. The pharmacological activity is accounted for by only one of the enantiomers. It is known that (R)-(−)-ibuprofen has substantially less pharmacological activity than (S)-(+)-ibuprofen. Since, however, the ineffective (R)-(−)-enantiomer is con-

Col. 1

Col. 1

verted to the active (S)-(+)-enantiomer in vivo, as has been proved by analysis of ibuprofen metabolites excreted in the urine, no therapeutic advantage has until now been expected from the use of the (S)-(+)-form instead of the racemate and a separation of the dextro rotatory form from the laevo rotatory form has not been thought to be necessary.

It has now been found that, contrary to established opinion, according to which the ibuprofen-racemate was the most suitable therapeutically-active form since the inactive (R)-(−)-enantiomer was converted into the active (S)-(+)-enantiomer in humans, that the (S)-(+)-form of ibuprofen, i.e. in the absence of the (R)-(−)-form has a substantially greater pharmacological potential than was anticipated. The present invention is based on this recognition.

The invention relates to an ibuprofen-containing medicament and is characterized in that in the medicament ibuprofen is only present as the (S)-(+)-enantiomer. It was not to be expected that by the sole use of the (S)-(+)-enantiomer a substantial reduction of dosage would be possible, since it was known that the as such largely inactive (R)-(−)-ibuprofen was converted into the active (S)-(+)-ibuprofen in humans. It was, however, surprisingly found that the same analgetic activity caused by a given dose of racemic ibuprofen can not only be achieved by half the dose of (S)-(+)-ibuprofen, but that even less than half as much (S)-(+)-ibuprofen as racemic ibuprofen is required to give a given analgetic activity. This result is, on the basis of observations until now on the mechanism of action of NSAR, particularly ibuprofen, extremely surprising. These

Evaluation of the Analgetic Activity of Ibuprofen

In this test the afferent nerves of the feet of female Rhesus monkeys were electrically stimulated. For the test four adult female Rhesus monkeys (macaca mulatta) were used.

The following active ingredients were used:

(S)-(+)-ibuprofen
(R)-(−)-ibprofen
(±)-ibuprofen
Acetylsalicylic acid

Col. 6

Each animal was treated with the following active ingredients in the given quantities:

1. (S)-(+)-ibuprofen	50 mg/kg
2. (R)-(−)-ibuprofen	50 mg/kg
3. (±)-ibuprofen	50 mg/kg
4. acetylsalicylic acid	100 mg/kg
5. carrier (0.5% carboxymethyl cellulose)	

Col. 6

TABLE 1

Percentage change of the voltage required to achieve a stimulus response in the female Rhesus monkeys

Treatment	Oral Dose (mg/kg)	Median percentage change in the threshold voltage at various times (h) after administration of the effective ingredient							
		0.5	1.0	1.5	2.0	2.5	3.0	4.0	5.0
Carrier	—	−6.6	−4.8	−13.0	−7.4	−4.3	−5.6	−11.5	−6.9
(+)-S-Ibuprofen	50	+9.5	+33.5*	+51.2*	+53.9	+45.5	+42.3	+33.7	+38.2
(−)-R-Ibuprofen	50	−5.7	−4.0	+4.5	+0.5	−4.7	−7.0	−2.3	−1.4
(+)-Ibuprofen	50	+6.4	+8.4	+15.7	+15.7	+8.5	+18.1	+9.7	+17.0
Acetylsalicylic Acid	100	+35.8	+56.6*	+41.4	+80.4	+74.6	+72.8	+66.1	+59.8

Statistical analyses carried out using the Mann-Whitney U Test
*P < 0.05 compared to the carrier

Mapelli discloses taste masking of an orally administered drug by coating the drug with a polymeric membrane soluble only at a pH of 5 of greater. An acid substance is included in the formulation to reduce or prevent the dissolution of the membrane in the oral cavity.

Reuter dislcoses

(a) Field of the Invention

This invention relates to a novel therapeutic form of spray dried ibuprofen having a neutral taste which can be formulated into, for example, chewable tablets and fast dissolving dosage forms as described in U.S. Pat. Nos. 4,305,502 and 4,371,516. More specifically this invention relates to a taste-neutral spray dried powder formed by spray drying a solution of ibuprofen and ethylcellulose, hydroxyethyl cellulose or hydroxypropylmethyl cellulose alone or in admixture, in at least a 50% lower alkanol solution having suspended therein colloidal silica. By taste-neutral it is meant that the powder has essentially no taste and is neither sweet nor bitter.

Col. 1

The use of flavor agents eg. chocolate, banana, orange, lemon, licorice, root beer, and raspberry, in particular, have been proposed for bitter tasting drugs. These agents are not dependable masking ingredients. Mint flavors can be useful in ameliorating a chalky taste parameter. Bitter properties, however, are very difficult to mask to any great extent, particularly, when they do not mimic the expected natural taste of the flavor agent.

Col.. 1

3

Food acids, eg. fumaric acid and malic acid, which are soluble in alkanol solutions and can create an aqueous environment not greater than pH 4.0, may correct the perception of bitterness in preparing the spray dried powder.

EXAMPLE 1

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient in suspension
Ibuprofen, USP	60.6	100
Hydroxyethyl Cellulose, NF	30.3	50
Colloidal Silica	6.06	10
Castor Oil	3.03	5
Isopropyl Alcohol, 67%	—	q.s 1000 ml
Total:	100%	1165 grams

The ibuprofen was dissolved in a portion of the alcohol contained in a stainless steel mixing vessel with the aid of a Lightnin mixer. The hydroxyethyl cellulose was wetted and dispersed in the remaining alcohol in a separate stainless steel mixing vessel with the aid of a Lightnin mixer. The contents of the two mixing vessels were filtered and combined. The castor oil and then colloidal silica were added and mixed until a homogeneous dispersion was obtained. The dispersion was then transferred to the feed hopper of the Buchi Mini Spray Dryer.

The spray dryer was operated such that an air inlet temperature of 153°-210° C. and an air outlet temperature of 94° to 108° C. was maintained throughout the run.

The yield of spray dried powder was about 90% of theoretical. The product was a white, fine powder.

The freshly obtained product upon tasting and being held in the mouth for 45 seconds produced no bitterness characteristic of ibuprofen. Upon aging one month at room temperature the product remained quite acceptable without bitterness.

EXAMPLE 2

This example describes the preparation of fast dissolving dosage forms using the spray dried taste-neutral ibuprofen of Example 1 and other ingredients as follows:

Col. 3

4

Ingredient	Weight % suspension	Grams in suspension
Gelatin, BY 150	4.0	10.00
Mannitol, granular	3.0	7.50
Deionized water	67.10	167.75
NUTRASWEET, NF	1.20	3.00
Cherry #271	0.40	1.00
Cream Flavor #59.200/A	0.20	0.50
Sodium lauryl sulfate	0.10	0.25
Croscarmellose sodium, Type A	1.00	2.50
Powder, Example 1	23.0	57.50

EXAMPLE 4

In this example, the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Weight % Solids in powder	Grams Ingredient per 100 ml of suspension
Ibuprofen, USP	53.2	125
Isopropyl Alcohol	—	200.00
Ethyl Cellulose, NF	21.3	50
Colloidal Silica	17%	40
Castor Oil	4.25	10
Fumaric Acid	4.25	10
Isopropyl Alcohol	—	q.s. 1000 mL
Total	100%	

EXAMPLE 5

In this example, ethyl alcohol was used instead of isopropyl alcohol and the feed mixture to the spray dryer was composed of the following materials.

Ingredient	Grams Ingredient per 1000 ml suspension	Weight % Solids in Powder
Ibuprofen USP	115	54.8
Ethyl Cellulose, NF	50	23.8
Colloidal Silica	25	11.9
Hydroxypropylmethyl Cellulose	5	2.4
Castor Oil	10	4.8
Fumaric Acid	5	2.4
Ethyl Alcohol	q.s. 1000 ml	100%

At the outset, claims 1-14 were cancelled in the August 5, 2003 Preliminary Amendment. It is believed that this rejection, as it pertains to claims 1-14, is moot. Therefore, the rejection is improper and should be withdrawn.

In making the rejection, the Examiner asserted that:

> The claims are directed toward an oral composition comprising a racemic mixture of ibuprofen or derivative and 50-150 wt% fumaric acid (or 60%, 7-13%). The claims are also directed toward the composition of ibuprofen wherein the drug are coated particles and comprise excipients and the polymeric coating is hydrocolloid. The claims are further drawn toward the composition in tablet, chewable dosage, liquid, suckable solid or semi-solid form, the composition reduces the burn sensation of ibuprofen.

(Office Action at 5.)

As mentioned, Loew et al (Patent '227) disclose a pharmaceutical composition comprising a racemic mixture of ibuprofen (col 6, lin 10-15, lin 50-60; col 7, Table 1; lin 60-65 and col12, lin 15-30).

Patent '227 does not teach the use of fumaric acid as excipients and does not teach that ibuprofen drug particles are used for making the composition.

We discussed Mapelli et al (WO '043) above. WO '043 discloses the use of polymer-coating before granulation (page 4, lin 10), discloses the use of polymer for coating (page 4, lin 24, continuing to page 5, lin 1-5) and discloses the use of excipients such as fumaric acid (page 2, lin 25-30; page 5, lin 1-6; page 6, lin 1-5 and page 12, lin claims 2-5; and page 12, claim 2). WO '043provides a method of masking the undesirable taste of the drugs by coating with polymeric membranes (page 2, lin 25-30 and page 13, claim 10). WO '043 discloses formulations of the drug such as tablet, sachet and formulation that is easily disintegrated in the mouth (page 6, lin 10).

Reuter et al (Patent '187) is relied upon for the disclosure of powdered ibuprofen composition comprising cellulose and hydroxyethyl cellulose, sodium lauryl sulfate and fumaric acid (col 4, lin 1-10, col 5, Example 4 and Example 5). Significantly, Patent '187 discloses that the composition is taste neutral (col3, lin 55-60 and col8, lin 10-15). (Office Action at 6.)

The Examiner reasoned that one of ordinary skill would have been motivated to prepare pharmaceutical composition comprising racemic mixture of ibuprofen- generally known to have an unpleasant taste- and mask such unpleasant taste by coating with polymeric membranes and/or adding excipients such as malic acid, fumaric acid. (Office Action at 6.) The Examiner further reasoned that one of ordinary skill would expect to obtain organoleptically acceptable compositions of ibuprofen that would [be] more appealing and suitable to patient taste and thereby improve patient compliance in taking medication. (*Id.* at 6-7.) The Examiner concluded that "the invention as a whole would have been obvious to one of ordinary skill in the art at the time it was made." (Office Action at 7.)

Initially, it is noted that claims 15-22 are directed to, among other things, a method for reducing the burn sensation of propionic acid derivative compositions. The rejection fails to identify where in any of the cited document such a limitation can be found.

As is fundamental, a *prima facie* case of obviousness must be based on facts, "cold hard facts." When the rejection is not supported by facts, it cannot stand.

The rejection uses facts related to compositions to reject method claims. It is not seen in this record where there are any facts to support such reasoning. Thus, the rejection is not supported by facts and must be withdrawn for this reason alone.

Even if the rejection were proper, which is denied, it ignores the fact that it appears that Loew teaches away from the claimed invention. In particular, Loew discloses advantages of using the (S)-(+)-ibuprofen over the racemic mixture or its racemate. It is not seen where one of ordinary skill in the art would be motivated to use racemic ibuprofen in the method of the claimed invention. Nor is it seen where Mapelli and Reuter provide the necessary motivation.

A *prima facie* case of obviousness, however, requires that the rejection describe with specificity **why** one skilled in the art would have combined two references to arrive at the claimed invention. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (CAFC 1999). ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of *the requirement for a showing of the teaching or motivation to combine prior art references*."). In the present case, no such explanation is found in the rejection. The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Thus, the rejection is not supported by the kind of specificity required to sustain a conclusion of obviousness. For this additional reason, the rejection is improper and should be withdrawn.

Finally, the Examiner is invited to call the applicants' undersigned representative if any further action will expedite the prosecution of the application or if the Examiner has any suggestions or questions concerning the application or the present Response. In fact, if the claims of the application are not believed to be in full condition for allowance, for any reason, the applicants respectfully request the constructive assistance and suggestions of the Examiner in drafting one or more acceptable claims pursuant to MPEP § 707.07(j) or in

making constructive suggestions pursuant to MPEP § 706.03 so that the application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,

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DATE: May 12, 2005